REMARKS

Claim Amendments

Claims 5-9, 11-15, 17-29, 31-35 and 38 were under consideration in the instant Office Action. Claims 5-9, 11-15, 17-29, 31-35 and 38 have been canceled. Claims 39-52 have been added. The newly added claims do not add or constitute new matter. Support for the amendments may be found throughout the specification and originally filed claims. More particularly, support for the target gene definition as recited in the newly added claims may be found, for example, at page 6, lines 18-29, particularly at lines 24-27, of the specification. Support for the phenotypes recited in the pending claims may be found, for example, at page 52, lines 12-16, page 53, lines 1-22 and at page 54, lines 8-12, of the specification. Support for the methods and uses recited for the transgenic mice may be found, for example, at page 18, line 28 through page 19, line 27 of the specification. As such, no new matter has been added.

The foregoing amendments are made solely to expedite prosecution of the instant application, and are not intended to limit the scope of the invention. Further, the amendments to the claims are made without prejudice to the pending or now canceled claims or to any subject matter pursued in a related application. Applicants reserve the right to prosecute any canceled subject matter at a later time or in a later filed divisional, continuation, or continuation-in-part application.

Upon entry of the amendment, claims 39-52 are pending in the instant application.

Applicants respectfully request reconsideration of the application in view of the amendments and remarks made herein.

Claim Objections

The Examiner has objected to claim 10 because it is dependent upon claim 1, drawn to a non-elected invention not currently under consideration. Applicants have overcome the objection by cancellation of claim 10.

Objections to the Specification

The Examiner has asserted that the description of Figures 2A-2B remains unclear after the amendment to its description filed December 4, 2002, and has indicated that the description should include the fact that the figure shows the nuclear hormone receptor of SEQ ID NO:1. Applicants believe that the previous amendment to the description of the figure does properly describe the figure as required by the Examiner. However, Applicants have submitted an amendment to the

description which attempts to address the Examiner's concerns regarding Figures 2A-2B. Therefore, Applicants believe that the objection is no longer relevant.

The changes made in the amendment to the specification are relative to the immediate prior version of the description to Figure 2A-2B filed December 4, 2002. The amendment is made merely to clearly identify the sequence disclosed in the Figure as SEQ ID NO:1. As such, no new matter has been added by this amendment. The amendment is supported by the originally filed specification, and more particularly, by the original description of Figure 2A-2B, and the sequences disclosed in Figure 1 and Figure 2A.

Rejection under 35 U.S.C. § 101

The Examiner has rejected claims 5-9, 11-15, 17-29, 31-35 and 38 under 35 U.S.C. § 101 because the claimed invention is allegedly not supported by either a specific or substantial asserted utility or a well-established utility. Applicants respectfully traverse the rejection. However, Applicants believe the rejection has been overcome in light of the amendments made herein and arguments presented below.

Claims 5-9, 11-15, 17-29, 31-35 and 38 have been canceled. New claims 39-52 are drawn to a transgenic mouse whose genome comprises a disruption in the nuclear hormone receptor mCAR, which results in a phenotype of impaired coordination or balance, a spleen abnormality, a thymus abnormality or a lymph node abnormality.

Applicants submit that in order to satisfy the utility requirements set forth in 35 U.S.C. § 101, the specification must assert a specific and substantial utility that is credible to a skilled artisan, or the utility of the claimed invention must be apparent to the skilled artisan. See MPEP § 2107. Applicants submit that the instant specification satisfies these requirements, particularly with respect to the invention recited in newly submitted claims 39-52.

Specifically, the specification has demonstrated that disruption of the target nuclear hormone receptor gene results in a specific phenotype, and, in particular, a phenotype of impaired coordination or balance, a spleen abnormality, a thymus abnormality or a lymph node abnormality. Several potential and credible uses for the transgenic mice have been disclosed in the specification. As an example, the specification has asserted that the transgenic mice are useful as a model for conditions or disorders associated with disruption of the target gene, such as the impaired coordination or balance, or organ abnormalities exhibited by the transgenic mice (see, for example, page 19, lines 6-16 and 23-27 of the specification). The skilled artisan would be capable

of using the mice to investigate or develop treatments, such as therapeutic compounds, which are able to ameliorate these conditions. Many other potential uses for the claimed mice would be readily apparent to the skilled artisan and are well-established in the art, as evidence by the demand for the production of transgenic mice comprising disruptions in virtually every gene. These include, but are not limited to, use as models for disease (*e.g.* a model of impaired coordination or balance, or of thymus, spleen or lymph node disorders), for identifying agents that ameliorate disease symptoms, for identifying agents that affect or modulate a phenotype caused by the gene disruption, or for determining the specificity of an agent targeting the nuclear hormone receptor gene mCAR (see, for example, page 18, lines 24-31, page 1, lines 6-16 and lines 23-27, and page 20, lines 7-14, of the specification). Applicants submit that these utilities of the claimed mouse would be immediately apparent to the skilled artisan, even absent Applicants' disclosure. The utility of transgenic knockout animals, and in particular mice, is well recognized in the art.

The instant Office Action appears to suggest that the only use for the claimed mice is as a model of disease, specifically as a model for neurological, neuropsychological, psychotic phenotypes. Further, the Office Action appears to also suggest that a neurological, neuropsychological or psychotic disease **found in humans** needs to be linked to the disruption produced in the target nuclear hormone receptor gene in order for the phenotypes in the mice to be considered useful. Applicants respectfully disagree with these conclusions. First, Applicants disagree that the sole utility asserted for the claimed mice is as a model for a human disease. As noted above, the transgenic mice can be used in several ways related to the phenotype of the claimed mice. Second, although it is believed that the phenotypes exhibited by the claimed mice are in fact linked to human conditions, disorders or diseases, Applicants are not aware of any such requirement in order to establish the utility of these mice.

Applicants submit that it is generally accepted in the art that transgenic knockout mice, such as those described in and claimed by the instant application, represent a valuable tool for determining the function of genes. In the present case, the transgenic mouse described in the instant specification would be recognized by the skilled artisan as a model for the physiological role of the target nuclear hormone receptor gene, mCAR, in conditions and disorders related to the phenotypes disclosed. Applicants' disclosure related to the phenotypes of the transgenic mice has established that this gene plays a role in the conditions or disorders of coordination, balance and immune system organ abnormalities such as in the spleen, thymus and lymph nodes, as noted

above, and has established the transgenic mice as models for discovering treatments or methods of modulating or ameliorating such conditions or disorders. The value of such an *in vivo* model would be immediately apparent to a person skilled in the art. This is supported by the homology between the mouse and human genomes, and the general acceptance that gene function in the mouse is related to and representative of that of humans.

However, even in the absence of a correlation between the phenotype(s) of the claimed mouse and a human disease or disorder, a link between the target nuclear hormone receptor gene disruption and the claimed phenotypes of impaired coordination or balance, spleen abnormality, thymus abnormality and lymph node abnormality **in a mouse** has been clearly established. The skilled artisan would easily recognize the utility or value of the transgenic mouse for studying or investigating conditions related to this gene in a mouse or related mammal. In this case, the skilled artisan could use the claimed mice to study the impaired coordination or balance or organ abnormalities in mice, and to discover or develop treatments for such conditions in mice or related animals. Each of these are clearly "real world" uses for the claimed transgenic mice that satisfy the utility requirements set forth in 35 U.S.C. § 101.

The Examiner has also asserted that the results of the behavioral tests, in particular the Rotarod test for coordination and balance, is not statistically significant because the number of mice tested is not disclosed. Applicants disagree with the Examiner's conclusions. However, the Applicants are not aware of any standard of statistical significance of a phenotype required for the establishment of patentability (utility) of a transgenic mouse. If such a standard exists, it is respectfully requested that the Examiner make the Applicants aware of the standard. Further, even if such a standard does exist, Applicants clearly disclosed in the instant application that a difference was observed between the transgenic mice and wild-type mice (see page 54, lines 8-12 of the specification). Applicants submit that this difference does exist. Therefore, Applicants believe that it is improper to reject the claimed mice based on the Examiner's allegation that there is not a statistical significance.

Applicants believe that the rejection under 35 U.S.C. § 101 for lack of a specific or substantial utility has been shown to be improper. Applicants have asserted in the specification several specific and substantial uses for the claimed transgenic mice, described above. Further, in light of the art-recognized value of and demand for transgenic knockout mice, the asserted utilities are among many that are well-established and credible to the skilled artisan. As a result,

Applicants do not believe that the Examiner has properly established that the claimed invention lacks a specific and substantial utility.

The Examiner's rejection of claims 5-9, 11-15, 17-29, 31-35 and 38 is no longer relevant as a result of the cancellation of these claims. Applicants submit that the rejection does not apply to newly submitted claims 39-52 for the reasons set forth above. Therefore, the rejection under 35 U.S.C. § 101 is no longer relevant, and Applicants respectfully request withdrawal of the rejection.

Rejection under 35 U.S.C. § 112, first paragraph

The Examiner has also rejected claims 5-9, 11-15, 17-29, 31-35 and 38 under 35 U.S.C. § 112, first paragraph, because one skilled in the art would allegedly not know how to use the claimed invention as a result of the alleged lack of either a specific or substantial asserted utility or a well-established utility set forth in the above utility rejection. Applicants respectfully traverse the rejection. However, for the reasons set forth above in response to the utility rejection, Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph, has been overcome. Therefore, Applicants respectfully request withdrawal of the rejection.

The Examiner has also asserted that the specification does not reasonably provide enablement for the transgenic mouse as claimed. The Examiner's enablement rejection relates to the unpredictability of a phenotype in a transgenic mouse, the state of the art of embryonic stem cell technology for germline transmission of a gene disruption, which is limited to the mouse system, and to use of the term "murine" which encompasses rats. The Examiner further alleges that the claims do not provide a nexus between disruption in the nuclear hormone receptor target gene and the phenotypes exhibited by the claimed mice. Applicants traverse each aspect of the rejection. However, the rejection has been overcome by the cancellation of claims 5-9, 11-15, 17-29, 31-35 and 38.

Applicants have submitted new claims 39-52, which are not relevant to the Examiner's enablement rejection. More particularly, the invention as recited in these claims addresses each of the Examiner's concerns by: (1) reciting a transgenic mouse or mouse cell, (2) reciting a detectable, useful phenotype resulting from disruption of the target gene, (3) reciting germline transmission of the gene disruption, and/or (4) cancellation of the claim(s). Therefore, Applicants submit that the rejection under 35 U.S.C. § 112, first paragraph, for enablement is no longer relevant, and request its withdrawal.

Rejection under 35 U.S.C. § 112, second paragraph

The Examiner has rejected claims 5-9, 11-15, 17-29, 31-35 and 38 under 35 U.S.C. § 112, second paragraph, for being indefinite for allegedly failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. Applicants respectfully traverse the rejection. Claims 5-9, 11-15, 17-29, 31-35 and 38 have been canceled, and the rejection is no longer relevant to these claims.

In one aspect, the Examiner asserts that the definition of "nuclear hormone receptor" genes is unclear. Applicants disagree. At page 6, lines 24-29 of the specification, Applicants define the term. Nowhere in this definition is the term or phrase "having homology with SEQ ID NO:1" present, as alleged by the Examiner. However, claims 39-52 clearly recite the gene or sequence disrupted in the present invention.

Claims 17-29 and 38 are allegedly indefinite in that they do not clearly set forth that the disruption in the nuclear hormone receptor gene causes the phenotype claimed. Applicants traverse the rejection. However, new claims 39-52 clearly recite that a phenotype exhibited by the claimed mice is a result of disruption of the target gene, the nuclear hormone receptor mCAR.

The Examiner has alleged that claims 21 and 26 are indefinite because it is unclear what "lymphoid depletion" is and whether it is relative term that requires comparison to another type of mouse. Applicants submit that the term lymphoid depletion is well-known in the art, and described in the specification as a reduction in number of lymphocytes (see, for example, page 53, lines 8-10). Further, the current pending claims set forth that this abnormality is relative to a wild-type mouse. As such, this rejection is not relevant to the pending claims.

Applicants' cancellation of claim 22 has rendered the rejection of this claim with regard to the term "periarteriolar lymphoid sheaths" irrelevant. The pending claims do not recite this term.

The Examiner has alleged that the phrase "consistent with" renders claims 27, 28 and 29 indefinite. This rejection is no longer relevant as new claims 39-52 do not recite this term. It is unclear to Applicants why claim 29 was included in this aspect of the rejection.

Applicants submit that the rejection under 35 U.S.C. § 112, second paragraph, has been overcome. Therefore, Applicants respectfully request withdrawal of the rejection. Applicants submit that new claims 39-52 clearly point out and distinctly claim that regarded as the invention as required by the second paragraph of 35 U.S.C. § 112.

Rejection under 35 U.S.C. § 102

Claims 5-9, 11-15, 17-29 and 31-35 have been rejected under 35 U.S.C. § 102(b) as being anticipated by Kato. (*J. Biochem* (May 2000) Vol. 127, Pages 717-722). Applicants respectfully traverse the rejection. However, as these claims have been cancelled, the rejection is no longer relevant.

According to the Examiner, Kato teaches mice having a disruption in the nuclear hormone receptor gene VDR. The Examiner has alleged that the VDR gene is a nuclear hormone receptor gene as encompassed by the above referenced claims because it shares homology with SEQ ID NO:1. Applicants, as noted above, disagree with the Examiner's interpretation of the definition of a nuclear hormone receptor, and do not believe that the claims encompass disruption of the gene as described by Kato. However, the rejected claims have been canceled. In light of the cancellation of claims and the reasons set forth below, Applicants have overcome this rejection.

To anticipate a claim, the reference must teach every element of the claim. "**A claim is anticipated [under §102] only if each and every element as set forth in the claim is found,** either expressly or inherently described, **in a single prior art reference.**" MPEP §2131 *citing* (Verdegaal Bros. V. Union Oil Co. of California, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987)).

The Applicants submit that Kato fails to teach each and every claim limitation as recited in new claims 39-52. More particularly, Kato fails to teach the transgenic mice whose genomes comprise a homozygous disruption in the gene encoding the nuclear hormone receptor mCAR disclosed in the instant application. Kato fails to teach or suggest the specific gene as described in the instant specification and recited in the pending claims. Furthermore, Kato fails to disclose that, as a result of disruption of any nuclear hormone receptor gene, particularly the gene recited in the pending claims, the transgenic mice exhibit a phenotype of impaired balance, a spleen abnormality, a thymus abnormality or a lymph node abnormality.

Therefore, the presently claimed invention is not anticipated by the disclosure of Kato, and the rejection is not relevant to claims 39-52. Applicants respectfully request withdrawal of the rejection udner 35 U.S.C. § 102(b).

Rejection under 35 U.S.C. § 103

Claims 5-9, 11-15 and 31-35 were rejected as being unpatentable under 35 U.S.C. § 103(a) based upon the teachings of Capecchi, 1994, *Scientific American,* Vol 270, pages 34-41, in view

of Choi, 1997, *J. Biol. Chem.*, Vol. 272, pages 23565-23571. Applicants respectfully traverse this rejection.

According to the Examiner, Capecchi teaches "a mouse having a disruption in a gene." Capecchi specifically describes disruption of the HoxA-3 gene and abnormalities associated with this disruption in mice. However, the Examiner even concedes that Capecchi fails to teach disruption of a nuclear hormone receptor gene, particularly the isoform as recited in the pending claims.

Choi merely dislcoses the nucleic acid sequence of the mouse nuclear hormone receptor gene described in SEQ ID NO:1 in the instant application. However, Choi clearly fails to teach or suggest any transgenic mice comprising disruptions in any gene, particularly the transgenic mice comprising disruptions in the gene encoding the nuclear hormone receptor mCAR as presently claimed.

As a basis of the obviousness rejection under 35 U.S.C. § 103, the Examiner asserts that one of ordinary skill in the art would have been motivated to disrupt the nuclear hormone receptor gene as described by Choi using the method disclosed by Capecchi in order to study the function of the nuclear hormone receptor *in vivo*. The Applicants respectfully disagree. However, in light of the cancellation of claims, the rejection is no longer relevant. As noted below, Applicants submit that the rejection does not apply to claims 39-52

In order to establish a *prima facie* case of obviousness, the Examiner must meet three basic criteria: there must be some suggestion or motivation to modify a primary reference or combine reference teachings; there must be a reasonable expectation of success; and the prior art reference(s) must teach or suggest all the claim limitations. See MPEP §2143. The Applicants contend that the prior art references cited by the Examiner are not sufficient to establish the presently claimed invention as *prima facie* obvious. Applicants submit that the disclosures of Capecchi and/or Choi, alone or in combination, fail to teach all of the limitations as recited in claims 39-52. Capecchi provides no disclosure or teaching of the nuclear hormone receptor gene described in the instant specification, and in particular does not disclose a specific phenotype found in transgenic mice comprising a disruption in said gene, particularly a phenotype of impaired coordination or balance, a spleen abnormality, a thymus abnormality and/or a lymph node abnormality, as claimed by the present invention. Likewise, Choi does not provide any

teaching or suggestion relating to a disruption in the mouse orphan nuclear hormone receptor gene as presently claimed, nor to disruption of any gene, for that matter.

Taken together, the disclosures Capecchi and Choi are devoid of any teaching or suggestion of the transgenic mice and cells as recited in the pending claims. More particularly, the combined disclosures of Capecchi and Choi do not teach or suggest in any way transgenic mice comprising disrupted mCAR nuclear hormone receptor genes, wherein such transgenic mice exhibit a phenotype of impaired coordination or balance, a spleen abnormality, a thymus abnormality or a lymph node abnormality. These references each do not make up for the deficiencies found in the other.

As the rejection under 35 U.S.C. § 103 is no longer relevant, and new claims 39-52 are not obvious in view of the sole or combined teachings of Capecchi and/or Choi, Applicants respectfully requests withdrawal of the rejection under 35 U.S.C. § 103.

It is believed that the claims are currently in condition for allowance, and notice to that effect is respectfully requested. The Commissioner is hereby authorized to charge any deficiency or credit any overpayment to Deposit Account No. 50-1271 under Order No. R-126.

Respectfully submitted,

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